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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/536,552	03/28/00	MASON A	9926-003-999

020583
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HM22/1023

EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	14

DATE MAILED: 10/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No. 09/536,552	Applicant(s) MASON ET AL.	
	Examiner Janet L. Epps	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-10* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

WILLIAM N. PHILLIPS
PATENT ANALYST wp

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The disclosure is objected to because of the following informalities: Page 8, line 27 recites the term "Pylogenetic tree," Applicants likely intended this term to recite "Phylogenetic tree." Page 10, line 4 recites "PSC patents," it is likely that Applicants intended this term to recite "PSC patients." Page 39, line 15, Table 5 recites the term "RT-PCT" it is likely that Applicants intended this term to be "RT-PCR".

Appropriate correction is required.

Response to Amendment

2. Claims 1, and 3-6 remain rejected, and claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the Official Action mailed 10-25-2000, and for the reasons set forth below.

Applicants have amended claim 1 to recite wherein the presence of the retroviral nucleic acid molecule of the present invention indicates that an individual has a disorder "related to" PSC, Autoimmune Hepatitis, Crohn's Disease, or ulcerative colitis. However, the specification as filed does not provide sufficient support for a method diagnosing conditions related to PSC, Autoimmune Hepatitis, Crohn's Disease, or ulcerative colitis. The specification only teaches wherein the method of the claimed invention is useful for diagnosing PSC, Autoimmune Hepatitis, Crohn's Disease, or ulcerative colitis, not conditions related to these. Applicant's

amendment is not commensurate in scope with the specification as filed. The specification as filed fails to provide proper antecedent basis for the limitation "related to" in the claims

Applicant's arguments filed 2-17-2001 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the PSC associated retrovirus is a unique sequence, and that the sequences used in the claimed method represent a limited number of nucleic acid sequences that have been clearly identified and characterized by Applicants. However, contrary to Applicant's assertions, claim 1 in particular does not recited the limitations regarding the unique sequences according to SEQ ID NO:1-7 described in the specification as filed. Moreover, the specification as filed contemplates other PSC associated retroviral sequences other than those represented by SEQ ID NO: 1-7. For example, in some alternative embodiments of the instant application, Applicants described the PSC associated retroviral sequences as comprising fragments of 20-1000 base pairs or more in length, however the sequences of the instant application range from 101 to 126 base pairs in length (see page 11, lines 35-37). Additionally, applicants describe the retroviral sequences of the present invention as including: genes which encode functionally equivalent sequences, naturally occurring PSC associated retroviral nucleotides present in the same or different species, sequences that hybridize to the complement of a nucleic acid molecule that encodes a PSC associated retroviral gene under moderately stringent conditions (page 11, lines 14-21), and various genome allelic variants of a PSC associated retroviral sequence and homologues isolated from other species (see page 12, lines 3-26).

Therefore, Applicant's assertion that the instant invention is limited to only those unique PSC associated retroviral nucleic sequences exemplified in the specification as filed, is not truly representative of the scope of the specification as filed or the breadth of the claimed invention.

3. Claims 5-6 remain rejected, and claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record set forth in the Official Action mailed 10-25-2000.

Applicant's arguments filed 2-17-2001 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that "[T]he invention as claimed is enabled. The specification particularly points out nucleic acid sequences specific to PSC associated retrovirus (page 100). It describes how antisense molecules, and ribozymes are effective at inhibiting PSC associated retrovirus, might be designed (pages 21-26). The state of the art is such that a skilled artisan would be able to practice the invention without undue experimentation." (See page 6, 2nd para. of Applicant's response.) Contrary to Applicant's assertions, the state of the art at the time of filing of the instant invention clearly indicate that one of skill in the art would not have been able to practice the full scope of the claimed invention without undue experimentation at the time of filing. As stated in the prior Official Action, there is a significant level of unpredictability in the art regarding the behavior of nucleic acid base therapeutics. According to Crooke (1998), variations in cellular uptake and distribution of oligonucleotides are influenced by a variety of factors, for example length of oligonucleotide, modifications to said oligonucleotide, sequence of oligonucleotide and cell type. Moreover,

Crooke clearly teaches that there are a significant number of factors which influence the behavior of nucleic acid based compounds thereby rendering the activity of nucleic acid based therapeutics unpredictable, and thus much experimentation is required to screen multiple nucleic acid compounds to determine not only their efficacy *in vitro* but also *in vivo*.

Applicants further traverse on the grounds that although the examiner cites several factors which complicate nucleic acid-based therapies, "[T]he *in vivo* consequences of altered gene expression does not apply in the instant case. The antisense molecules are specific and directed toward a PSC associated retroviral sequence. Altered gene expression is only a factor when the sequence is directed toward a portion of the endogenous genome." However, contrary to Applicant's assertions, the instant claims do not recite wherein the antisense or ribozyme molecules are specific toward a PSC associated retroviral sequence, the instant claims recite "a composition which targets a PSC pol sequence." The claims do not require that the antisense, ribozyme, or any other composition be specific for a PSC pol sequence. Additionally, as stated above the PSC associated retroviral sequences of the instant invention encompass genome allelic variants of said sequences (see page 12, lines 3-26). Furthermore, Applicants have not provided any evidence that the antisense or ribozyme compositions of the present invention would somehow be immune to the various factors which contribute to the unpredictability associated with antisense based compounds in cellular environments as described in the prior Official action. Applicants merely assert that their claimed method is enabled based upon observations in the Crooke (1998) reference that indicate that antisense molecules have been used in a therapeutic fashion in the art. However, as stated previously, the behavior of the particular antisense oligonucleotide compositions described in Crooke (1998) comprising a sequence and

modifications distinct from those set forth in the instant application, can not be used to predict the usefulness of the compositions of the present invention, since the length of oligonucleotide, modifications to said oligonucleotide, sequence of oligonucleotide and cell environment play a critical role in controlling the behavior of antisense oligonucleotides within a cell (see Crooke (1998)). Furthermore, it is unclear how one of skill in the art would use the teachings of the specification as filed in light of the Crooke (1998) reference to practice the full scope of the claimed invention without undue experimentation, since Applicants have not provided any working *in vitro* or *in vivo* examples, nor have they provided any evidence that the compositions of the present invention would be particularly useful in a therapeutic manner.

Moreover, Applicants argue that although some experimentation would be required to practice the claimed invention, "[E]nablement is not precluded, even if some experimentation is necessary." However, enablement is precluded when the amount of experimentation required is "undue", the nature of the experimentation is "unpredictable," the Applicants do not provide any working examples, the genus of compounds used in the claimed invention is very broad (as described in the above rejection), and the specification as filed has not provided sufficient guidance and/or instruction to teach one of skill in the art specifically how to overcome the various factors which influence the behavior of antisense oligonucleotides *in vitro* or *in vivo*.

4. Claim 1 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Mason et al. in view of Peterson et al; and Claims 3-4 remain rejected under 35 U.S.C. 102(e) as being Peterson et al. as evidence by Mason et al., for the reasons of record set forth in the Official Action mailed 10-25-2000.

Applicant's arguments have been fully Applicant's arguments filed 2-22-01 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that "[N]othing in either Mason or Peterson suggests the unique sequence associated with a PSC retrovirus which Applicants have disclosed in their specification and is the subject matter of claim 1."

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the unique sequences associated with a PSC retrovirus) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Additionally, Applicants argue that "a skilled artisan would not have a reasonable expectation of success in the development of a method to detect a unique PSC associated retrovirus." Again, the instant claims do not recite "a unique PSC associated retrovirus."

Moreover, applicants argue that Mason does not provide a direct link between the presence of PSC in an individual and HIV-1 infection, and furthermore that nothing in Peterson suggests that amplifying HIV-1 specific nucleic acid would be effective in recognizing PSC associated retroviral sequences. However, Applicant's own specification indicates that HIV-1 is related to the PSC retrovirus (see Figure 1). Since the instant claims are not limited to the PSC retroviral sequences according to SEQ ID NO:1-7, the instant claims broadly read on any PSC related retroviral sequences, and therefore the HIV-1 retroviral sequence would inherently qualify as a PSC associated retrovirus. Furthermore, Applicants have not provided any credible evidence that would question the validity of the teachings of Mason et al. which clearly provide a

strong correlation between the presence of HIV-1 nucleic acid in a sample and the presence of an autoimmune disease in a patient. Moreover, Applicants state that "[T]he mere fact that some PSC patients have an antibody that cross-reacts with a different retrovirus can hardly be considered to be a 'method of identifying individuals with PSC,' particularly when the majority of patient's samples do not cross-react." However, Applicant's experimental results in Table 4 (page 38) using the PSC retroviral primers and probe, showed only 1 out of 13 samples wherein they obtained a positive PCR result, and furthermore they did not observed hybridization of the PSC probe in any of the samples. The observations in Mason et al. were more conclusive than Applicants data in this instance. In regards to Applicants data in Table 5, there is some positive data, however Applicant's results are somewhat confusing since it is unclear what sequence Applicants used for hybridization analysis. Table 4 recites the use of PSC primers and probe, however Table 5 recites the use of "Potential PSC Related Viral cDNA Fragment."

Additionally, Applicants argue that the rejection of claims 3-4 under 35 USC 102(e) should be withdrawn since the rejection is in error. Furthermore, Applicants claim that "[T]he legal test for anticipation under 35 USC 102 requires that the prior art meet every element of the claimed invention, and such a determination is one of fact." However contrary to Applicant's arguments the instant claims are not limited to the unique PSC associated retroviral nucleic acid molecules according to SEQ ID NO: 1-7, the instant claims broadly read on any PSC associated retroviral sequence. As described above, this includes sequences comprising only a fragment of the sequences according to the instant invention (101 to 126 base pairs in length), further comprising up to 1000 base pairs, genomic alleic variants, and variants from other species. Since the claimed invention essentially reads on any retrovirus associated with PSC, autoimmune

hepatitis, Crohn's disease or ulcerative colitis, absent evidence to the contrary HIV-1 retroviral nucleic acid would also qualify as a PSC associated retrovirus since Mason et al. does show correlation between HIV and autoimmune diseases.

5. Claims 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites "the PSC associated retrovirus" and the "virus". There is insufficient antecedent basis for these limitations in this claim.

Claim 8 recites "the PSC associated retrovirus", "the PSC pol sequence" and the "virus". There is insufficient antecedent basis for these limitations in this claim.

Conclusion

6. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps whose telephone number is 703-308-8883. The examiner can normally be reached on Mondays through Friday, 9:00AM to 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps
Examiner
Art Unit 1635

JLE

October 15, 2001

SEAN McGARRY
PRIMARY EXAMINER